Remarks

In the Office Action dated August 1, 2003, claims 24-39 in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 24-25, 27-28 and 30-39 remain in this application, claims 1-23, 26 and 29 have been canceled.

Claims 24-39 were rejected under 35 USC §112 as lacking enablement for fragments which are not immunogens. The claims have been amended to clarify that the fragments are immunogens.

Claims 24, 26-29, 31 and 33 were rejected under 35 USC §112, second paragraph as indefinite. Claims 26 and 29 have been canceled and the remaining claims amended to clarify the language found indefinite. In view of these amendments applicants request that these rejections be withdrawn.

Claims 24-26 and 29-39 were rejected under 35 USC §102(b) as anticipated by Fulginiti. Applicants respectfully point out that there is no disclosure of a protective vaccine in Fulginiti. To applicant's knowledge, there is no paper by Fulginiti or his group relating to this abstract. Thus, it cannot be determined from Fulginiti's disclosure whether "urease" means urease A, B or both. In addition, no details of the expression system pPX5024 are indicated. pP X5024 is a plasmid which, to applicant's knowledge, is not commonly used and its sequence cannot be obtained from common text books. Applicant's contend that since the protein to be expressed and the expression system are

essential features, the Salmonella strain of Fulginiti is not enabled by the cited disclosure.

Fulginiti describes antibody formation which does not indicate a protective effect because such antibodies can be found in many patients suffering from Helicobacter infection. Fulginiti does not provide any data demonstrating a protective effect. The last sentence of the Abstract ("Studies are underway to characterize...") indicates that experiments relating to protection were incomplete. Since the results of these experiments were never published, it can be concluded that they were either unsuccessful or they were not completed for other reasons. Vaccine development against Helicobacter is still an attractive field of research. If Fulginiti had been successful he would have published his results in a scientific journal, as did the inventors of the present invention. Applicants point out that Fulginiti's Salmonella strain is "immunoreactive" rather than being an "immunogen". Since immunogenicity is an essential feature of the claimed subject matter, Fulginiti does not anticipate the present claims. In addition, there is no indication in the Abstract that Fulginiti used both urease A and urease B as recited in the present claims.

Claims 24, 26, 29 and 30-39 were rejected under 35 USC §102(e) as anticipated by Michetti (U.S. Pat. No. 6,290,962). Applicants respectfully point out that Michetti discloses the use of both subunits **separately** in the production of the vectors. Michetti used the subunits separately and does not specifically suggest that they be used together. Table 6 (summarizing the data of Table 4) suggests that there is a fast UreB response and a slower UreA response. Thus, a

combination of UreA and Ure B could possibly lead to an improved vaccine with short- and long-term protectivity. However, this expectation was not confirmed by an additional experiment described in columns 26 and 27, (raw data in Table 7) based on the same protocol as the data of Tables 4 to 6, but using an alternative method of analysis. This analysis method was also applied to the data of Table 4. The combined data indicate that 12 days post-challenge UreA does not elicit an immune response. 70% of animals immunized with UreA showed a low grade infection. More importantly, 10 weeks post-challenge, protection is observed in about 60% of mice immunized with UreA, but in 80% of mice immunized with UreB. From this data it must be concluded that UreB has a better performance at both 12 days and 10 weeks post-challenge. In the combined data of Tables 4 and 7, there is no indication that UreA protection exceeds UreB protection. Since this interpretation is in contrast to the conclusion drawn from the data of Tables 4 to 6 alone, a person skilled in the art would consider the interpretation of the combined data to be the correct one (because it is derived from a larger set of data). Native urease leads to a protection of 70% (see Table 2, protocol B in the column 28, 5 or 7 days after challenge). Based on Michetti, a person skilled in the art would expect that the combination of recombinant UreA and UreB would result in a protection similar to that of native urease. Since recombinant UreB exhibits a better protection than native urease, a person skilled in the art would not consider the combination of UreA and UreB in view of Michetti's disclosure.

The sections of Michetti cited in the office action (col.19, lines 63-67 and col 20, lines 1-3) indicate only that both subunits were produced, not that they were used together. Col. 20, lines 7-11, indicate that urease A or urease B was administered, not both subunits together. Tables 5, 6 and 7 indicate that the subunits were administered separately. Col. 25, lines 58-67 compares the results obtained using the separate subunits. Table 2 provides the results of immunization with purified urease not a recombinant cell. One cannot determine which subunit (or both subunits) is providing protection when the purified urease is administered.

In addition, applicants point out that the subunit immunization approach for purified urease and urease subunits described by Michetti depends on antibody-mediated (IgA) mucosal immune response. This mechanism was generally thought to be relevant for protective immunity against Helicobacter infection. Thus, Michetti only discloses bacterial cells which are able to mimic the protective effect of native urease or a urease subunit delivered to the mucosal surface. Since there is no specific disclosure of Salmonella cells expressing Helicobacter antigens in Michetti, a skilled person might assume that the recombinant urease is delivered by surface exposure and secretion. Michetti describes how much antigen is needed for successful vaccination. He uses an enriched fraction of recombinant urease purified from a bacterial lysate. A skilled person might doubt whether this can be achieved with recombinant Salmonella for two reasons: (1) the numerous antigens of the bacterium might compete with the urease antigen, thereby reducing urease specific immune response.

Applicant's point out that Michetti shows much better protection with purified and enriched urease in comparison to an orally administered Helicobacter lysate (see Table 2); and (2) the amount of antigen which is needed to provoke a protective immune response is rather high (30 µg, see columns 28 and 29) and one might wonder whether this quantity of secreted or surface-exposed urease can be achieved at all by a recombinant Salmonella cell. In any case, Michetti does not provide instructions on how to do this. Thus, Michetti does not suggest a live vaccine approach which achieves a protective immune response similar to the subunit approach as described by Michetti.

In the present invention, the route of immunization generally provokes a cellular immune response which differs from the protective humoral immune response described by Michetti. The immunoprotection of the present invention does not correlate with humoral anti- UreA and UreB response, suggesting that, in addition to humoral immunity, cellular immunity may be critical for protection (page 18 of the present application). Furthermore, considerably higher levels of urease activity were observed in mice immunized with recombinant UreB plus cholera toxin, compared with immunization with recombinant Salmonella cells (pages 18/19 of the description). Michetti does not disclose recombinant Salmonella cells which have the urease intracellularly. Michetti also does not suggest that an additional protection mechanism exists which leads to a recombinant live vaccine. Since Michetti does not disclose the use of a recombinant cell which includes a nucleic acid molecule encoding both subunits,

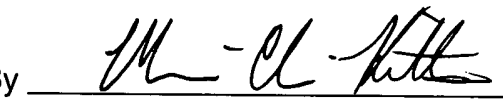
Michetti does not anticipate the present claims and applicants request that this rejection be withdrawn.

Claims 24, 26, and 33-35 were rejected as anticipated by Michetti (WO95/22987). Michetti does not disclose the use of a recombinant Salmonella cell which includes nucleic acids encoding both subunits and thus does not anticipate the present claims. For the same reasons discussed above regarding Michetti (U.S. Pat. No. 6,290,962), one would not use both subunits in view of Michetti's disclosure that subunit B is sufficient for protection and subunit A produces delayed protection. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 24-29 and 33-35 were rejected under 35 USC §103 as obvious over Michetti (WO95/22987) in view of Russell. Russell does not disclose the use of a recombinant Salmonella cell which includes nucleic acids encoding both subunits and thus does not cure the deficiencies discussed above regarding Michetti. In view of the above discussion, applicants contend that claims 24-29 and 33-35 would not have been obvious over the combination of Michetti and Russell and request that this rejection be withdrawn.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By 

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